

What is claimed is:

- 5 1. A method of inhibiting HDAC-4 activity in a cell, comprising contacting the cell with an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-4, whereby HDAC-4 activity is inhibited.
- 10 2. The method according to claim 1, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that is a chimeric oligonucleotide.
3. The method according to claim 1, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that is a hybrid oligonucleotide.
- 15 4. The method according to claim 1, wherein the antisense oligonucleotide has a nucleotide sequence of from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.
- 20 5. The method according to claim 1, wherein the antisense oligonucleotide has a nucleotide sequence of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

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6. The method according to claim 1, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that is SEQ ID NO:11.

7. The method according to claim 1, whereby inhibition of HDAC-4 activity in the contacted cell further leads to an inhibition of cell proliferation in the contacted cell.

8. The method according to claim 1, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth retardation of the contacted cell.

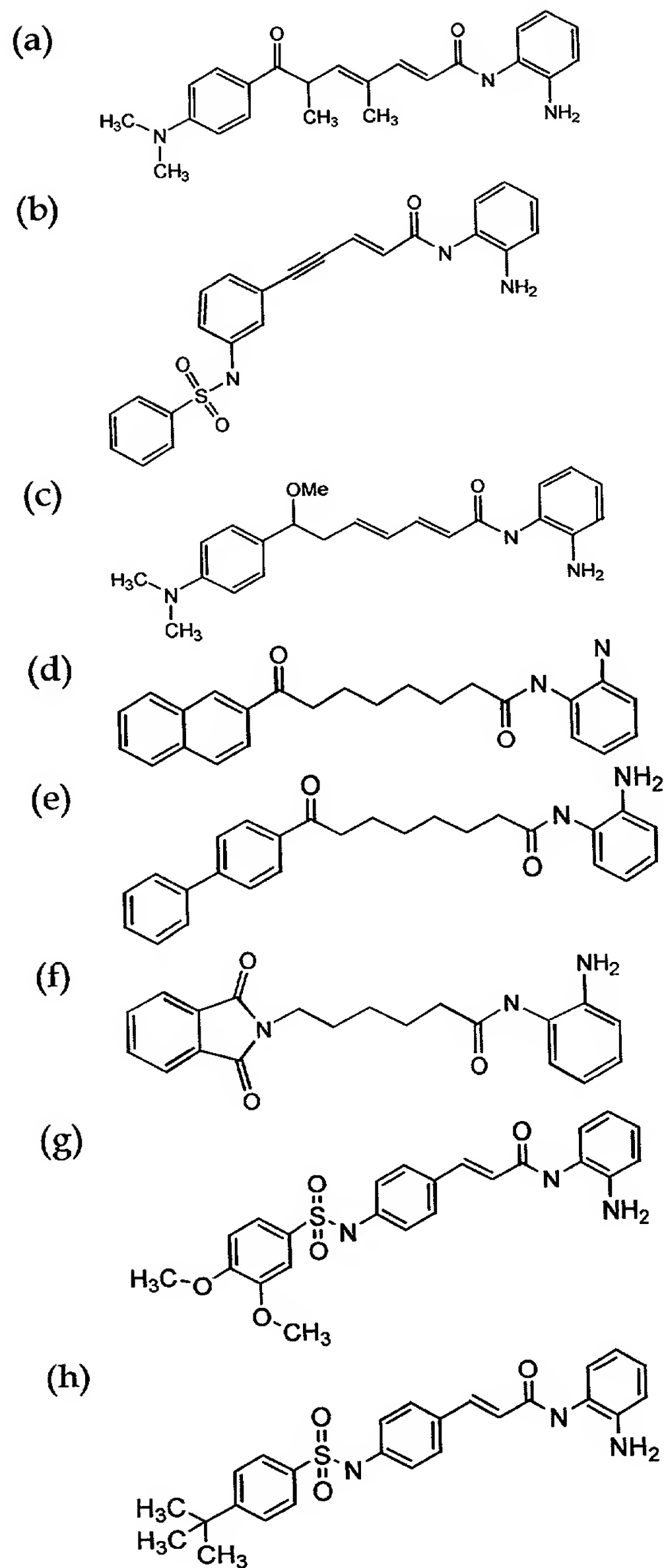
9. The method according to claim 1, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth arrest of the contacted cell.

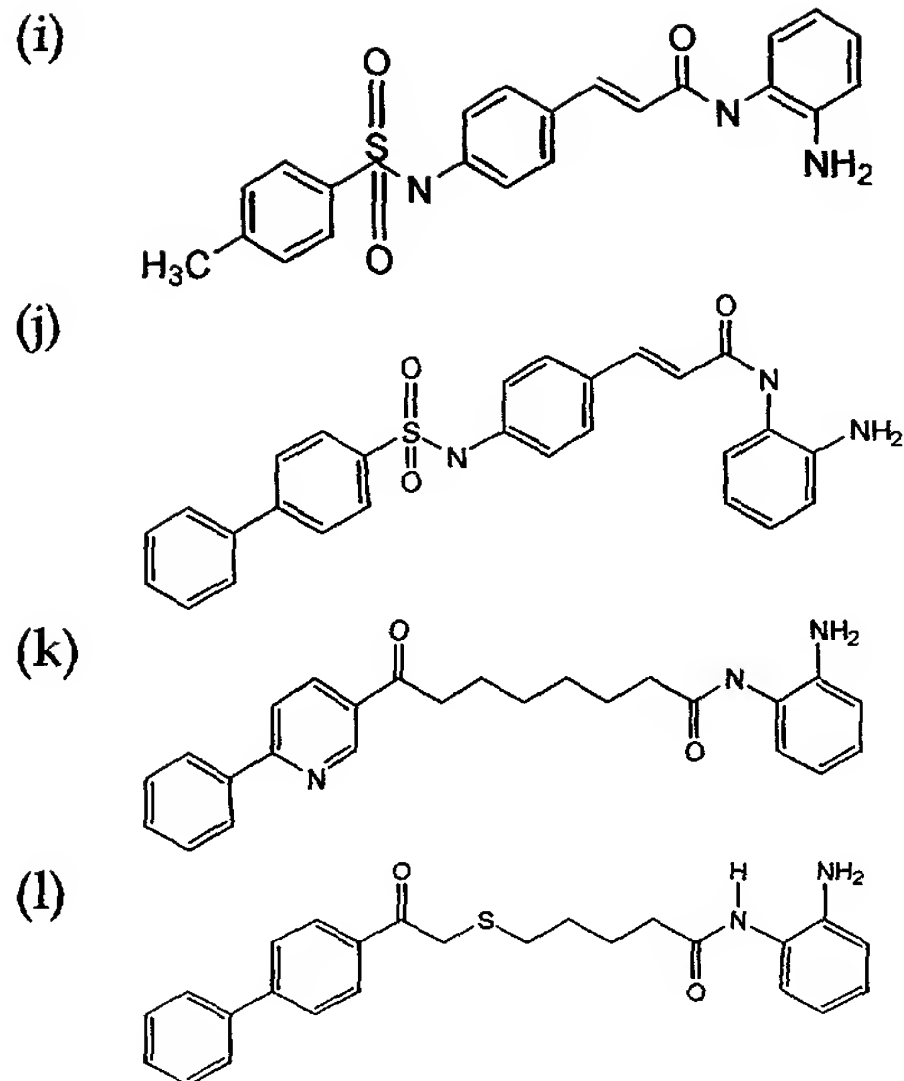
10. The method according to claim 1, wherein inhibition of HDAC-4 activity in the contacted cell further leads to programmed cell death of the contacted cell.

11. The method according to claim 8, wherein inhibition of HDAC-4 activity in the contacted cell further leads to necrotic cell death of the contacted cell.

12. A method of inhibiting HDAC-4 activity in a cell, comprising contacting the cell with a small molecule inhibitor of HDAC-4 selected from

the group consisting of:





13. The method according to claim 12, whereby inhibition of HDAC-4 activity in the contacted cell further leads to an inhibition of cell proliferation in the contacted cell.

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14. The method according to claim 12, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth retardation of the contacted cell.

15. The method according to claim 12, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth arrest of the contacted cell.

16. The method according to claim 12, wherein inhibition of HDAC-4

activity in the contacted cell further leads to programmed cell death of the contacted cell.

17. The method according to claim 13, wherein inhibition of HDAC-4
5 activity in the contacted cell further leads to necrotic cell death of the contacted cell.

18. A method for inhibiting neoplastic cell proliferation in an animal,
comprising administering to an animal having at least one neoplastic cell
10 present in its body a therapeutically effective amount of an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-4, whereby neoplastic cell proliferation is inhibited.

19. The method according to claim 18, wherein the animal is
15 administered a chimeric HDAC-4 antisense oligonucleotide.

20. The method according to claim 18, wherein the animal is
administered a hybrid HDAC-4 antisense oligonucleotide.

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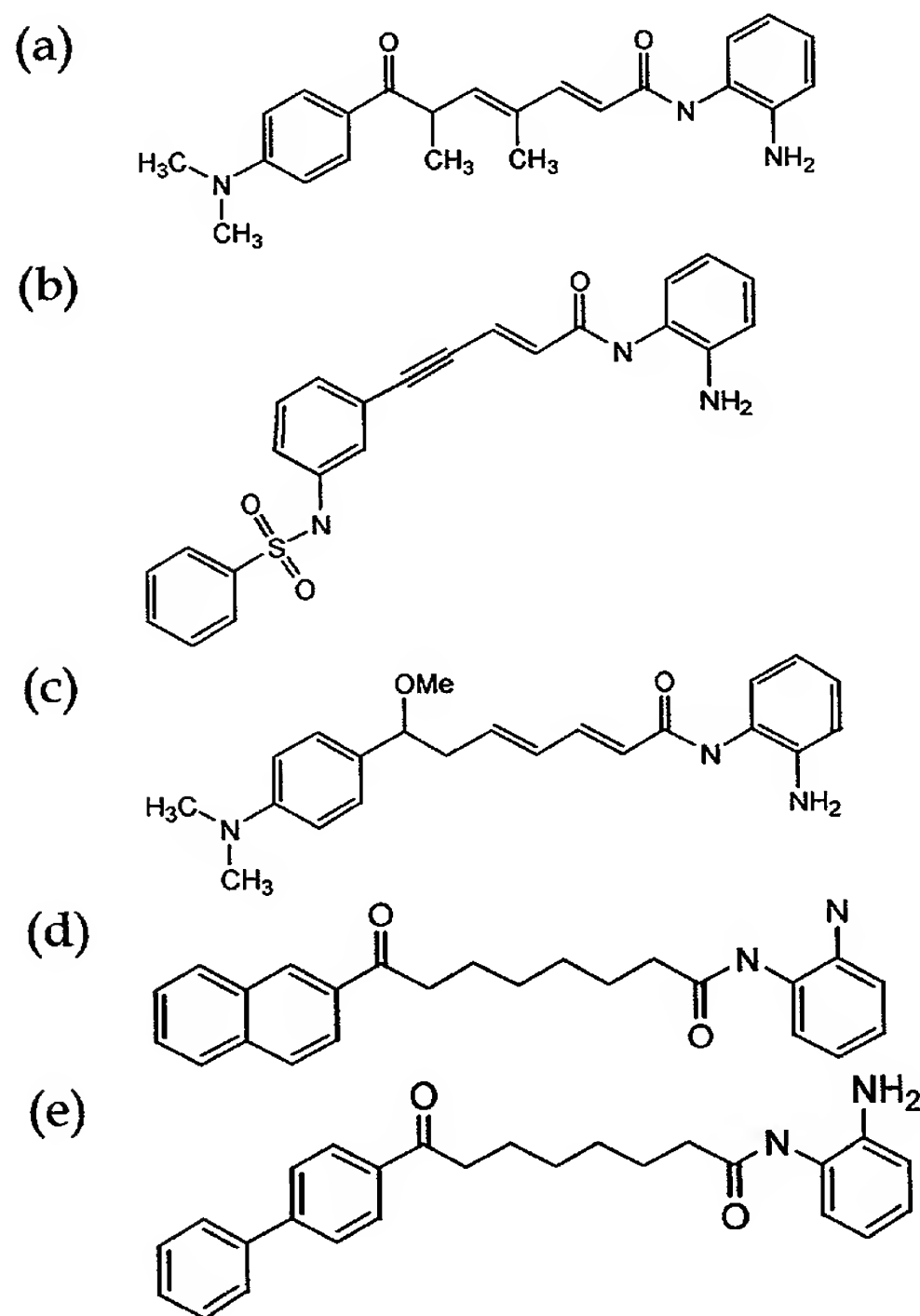
21. The method according to claim 18, wherein the antisense oligonucleotide has a nucleotide sequence of from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

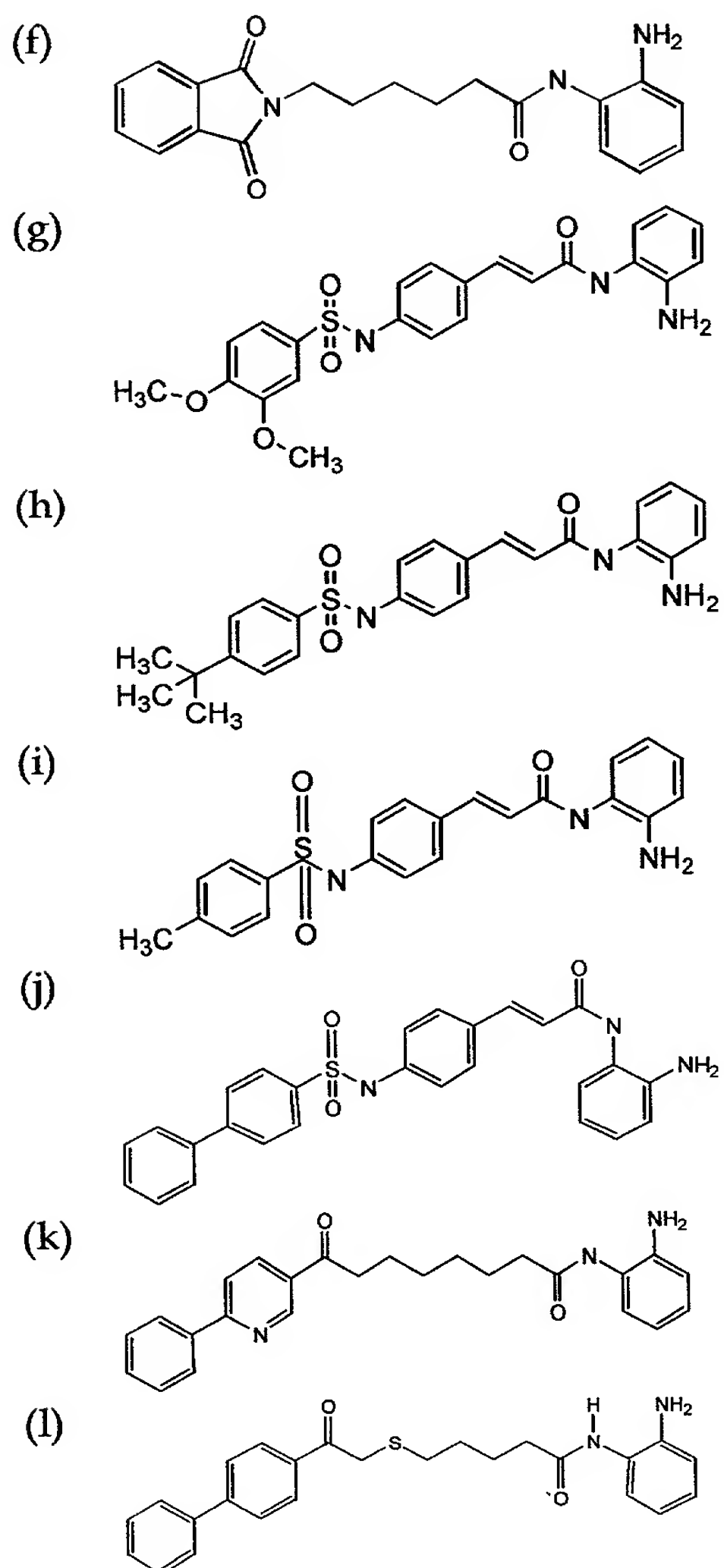
22. The method according to claim 18, wherein the antisense oligonucleotide has a nucleotide sequence of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.
- 5 23. The method according to claim 18, wherein the antisense oligonucleotide has a nucleotide sequence of from about 20 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.
- 10 24. The method according to claim 18, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that is SEQ ID NO:11.
- 15 25. The method according to claim 18, whereby inhibition of HDAC-4 activity in the contacted cell further leads to an inhibition of cell proliferation in the contacted cell.
- 20 26. The method according to claim 18, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth retardation of the contacted cell.
27. The method according to claim 18, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth arrest of the contacted cell.
- 25 28. The method according to claim 18, wherein inhibition of HDAC-4 activity in the contacted cell further leads to programmed cell death of the

contacted cell.

29. The method according to claim 25, wherein inhibition of HDAC-4 activity in the contacted cell further leads to necrotic cell death of the contacted cell.

30. A method for inhibiting neoplastic cell proliferation in an animal, comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a small molecule inhibitor selected from the group consisting of:





31. The method according to claim 30, whereby inhibition of HDAC-4 activity in the contacted cell further leads to an inhibition of cell proliferation in the contacted cell.

32. The method according to claim 30, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth retardation of the contacted cell.
- 5 33. The method according to claim 30, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth arrest of the contacted cell.
- 10 34. The method according to claim 30, wherein inhibition of HDAC-4 activity in the contacted cell further leads to programmed cell death of the contacted cell.
- 15 35. The method according to claim 31, wherein inhibition of HDAC-4 activity in the contacted cell further leads to necrotic cell death of the contacted cell.
36. The method according to claim 18 or 30, wherein the animal is a human.
- 20 37. The method according to claim 18 or 30, further comprising administering to an animal a therapeutically effective amount of an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-1.

38. The method according to claim 37, wherein the animal is administered a chimeric HDAC-1 antisense oligonucleotide.

39. The method according to claim 37, wherein the animal is administered a hybrid HDAC-1 antisense oligonucleotide.

40. The method according to claim 37, wherein the animal is administered an HDAC-1 antisense oligonucleotide having a nucleotide sequence of from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:2.

41. The method according to claim 37, wherein the animal is administered an HDAC-1 antisense oligonucleotide having a nucleotide sequence of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:2.

42. The method according to claim 37, wherein the animal is administered an HDAC-1 antisense oligonucleotide having a nucleotide sequence of from about 20 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:2.

43. The method according to claim 37, wherein the animal is administered an HDAC-1 antisense oligonucleotide that is SEQ ID NO:5.

44. A composition comprising an agent that specifically inhibits the

activity of HDAC-4.

45. The composition according to claim 1, wherein the agent is an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-4.

46. The composition according to claim 2, wherein the antisense oligonucleotide is a chimeric oligonucleotide.

47. The composition according to claim 2, wherein the antisense oligonucleotide is a hybrid oligonucleotide.

48. The composition according to claim 2, wherein the antisense oligonucleotide has a nucleotide sequence of from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

49. The composition according to claim 2, wherein the antisense oligonucleotide has a nucleotide sequence of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

50. The composition according to claim 2, wherein the antisense oligonucleotide has a nucleotide sequence of from about 20 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

51. The composition according to claim 2, wherein the antisense

oligonucleotide is SEQ ID NO:11.

52. The composition according to claim 2, wherein the antisense oligonucleotide has one or more phosphorothioate internucleoside linkages.

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53. The composition according to claim 9, wherein the antisense oligonucleotide further comprises a length of 20-26 nucleotides.

54. The composition according to claim 10, wherein the oligonucleotide is modified such that the terminal four nucleotides at the 5' end of the oligonucleotide and the terminal four nucleotides at the 3' end of the oligonucleotide each have 2' -O- methyl groups attached to their sugar residues.

55. The composition according to claim 1, wherein the agent is a small molecule inhibitor of HDAC-4.

56. The composition according to claim 12, wherein the structure of the small molecule inhibitor is selected from the group consisting of:

(a) $\text{Cy-CH(OMe)-Y}^1\text{-C(O)-NH-Z}$ (1)

wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; Y¹ is a C₄ - C₆ alkylene, wherein said alkylene may be optionally substituted and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected from the group consisting of O; NR¹, R¹ being alkyl, acyl or hydrogen; S;

S(O); or S(O)₂; and Z is selected from the group consisting of anilinyll, pyridyll, thiadiazolyll and -O-M, M being H or a pharmaceutically acceptable cation, wherein the anilinyll or pyridyll or thiadiazolyll may be optionally substituted;

5 (b) Cy-Y²-C(O)-NH-Z (2)

wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; Y² is C₅ - C₇ alkylene, wherein said alkylene may be optionally substituted and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected
10 from the group consisting of O; NR¹, R¹ being alkyl, acyl or hydrogen; S; S(O); or S(O)₂; and Z is anilinyll or pyridyll, or thiadiazolyll, any of which may be optionally substituted;

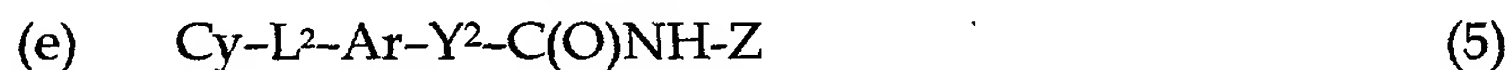
(c) Cy-B-Y³-C(O)-NH-Z
(3)

15 wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; B is selected from the group consisting of -CH(OMe), ketone and methylene; Y³ is a C₄ - C₆ alkylene, wherein said alkylene may be optionally substituted and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected
20 from the group consisting of O; NR¹, R¹ being alkyl, acyl or hydrogen; S; S(O); or S(O)₂; and Z is selected from the group consisting of anilinyll, pyridyll, thiadiazolyll and -O-M, M being H or a pharmaceutically acceptable cation, wherein the anilinyll or pyridyll or thiadiazolyll may be optionally substituted;

25 (d) Cy-L¹-Ar-Y¹-C(O)-NH-Z (4)

wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of

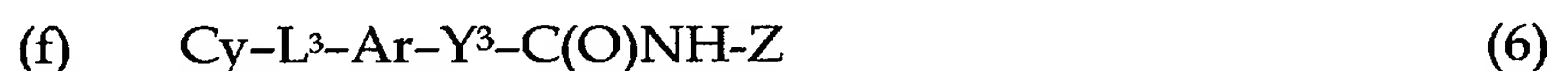
which may be optionally substituted; L¹ is -(CH₂)_m-W-, where m is 0, 1, 2, 3, or 4, and W is selected from the group consisting of -C(O)NH-, -S(O)₂NH-, -NHC(O)-, -NHS(O)₂-, and -NH-C(O)-NH-; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; Y¹ is a chemical bond or a straight- or branched-chain saturated alkylene, wherein said alkylene may be optionally substituted; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl, and -O-M, M being H or a pharmaceutically acceptable cation; provided that when L¹ is -(O)NH-, Y¹ is -(CH₂)_n-, n being 1, 2, or 3, and Z is -O-M, then Cy is not aminophenyl, dimethylaminophenyl, or hydroxyphenyl; and further provided that when L¹ is -C(O)NH- and Z is pyridyl, then Cy is not substituted indoliny;



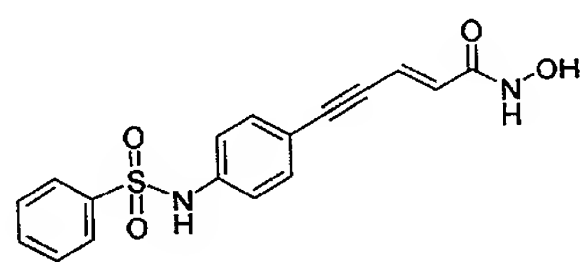
wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocycl, any of which may be

optionally substituted, provided that Cy is not a spirocycloalkyl)heterocycl; L² is C₁-C₆ saturated alkylene or C₂-C₆ alkenylene, wherein the alkylene or alkenylene optionally may be substituted, provided that L² is not -C(O)-, and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected from the group consisting of O; NR', R' being alkyl, acyl, or hydrogen; S; S(O); or S(O)₂; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; and Y² is a chemical bond or a straight- or branched-chain saturated alkylene, which

may be optionally substituted, provided that the alkylene is not substituted with a substituent of the formula $-C(O)R$ wherein R comprises an α -amino acyl moiety; and Z is selected from the group consisting of anilinyll, pyridyl, thiadiazolyl, and $-O-M$, M being H or a pharmaceutically acceptable cation; provided that when the carbon atom to which Cy is attached is oxo substituted, then Cy and Z are not both pyridyl;

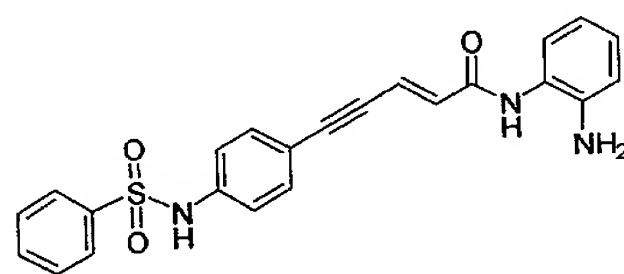


wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted, provided that Cy is not a spirocycloalkyl)heterocyclyl; L^3 is selected from the group consisting of (a) $-(CH_2)_m-W-$, where m is 0, 1, 2, 3, or 4, and W is selected from the group consisting of $-C(O)NH-$, $-S(O)_2NH-$, $-NHC(O)-$, $-NHS(O)_2-$, and $-NH-C(O)-NH-$; and (b) C_1-C_6 alkylene or C_2-C_6 alkenylene, wherein the alkylene or alkenylene optionally may be substituted, provided that L^3 is not $-C(O)-$, and wherein one of the carbon atoms of the alkylene optionally may be replaced by O; NR' , R' being alkyl, acyl, or hydrogen; S; $S(O)$; or $S(O)_2$; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; and Y^3 is C_2 alkenylene or C_2 alkynylene, wherein one or both carbon atoms of the alkenylene optionally may be substituted with alkyl, aryl, alkaryl, or aralkyl; and Z is selected from the group consisting of anilinyll, pyridyl, thiadiazolyl, and $-O-M$, M being H or a pharmaceutically acceptable cation; provided that when Cy is unsubstituted phenyl, Ar is not phenyl wherein L^3 and Y^3 are oriented *ortho* or *meta* to each other;



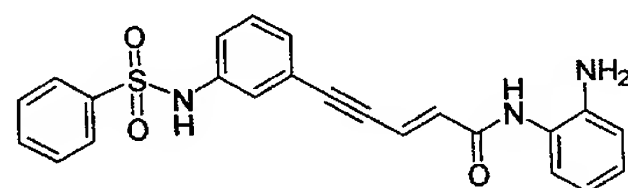
(e)

(7)



(f)

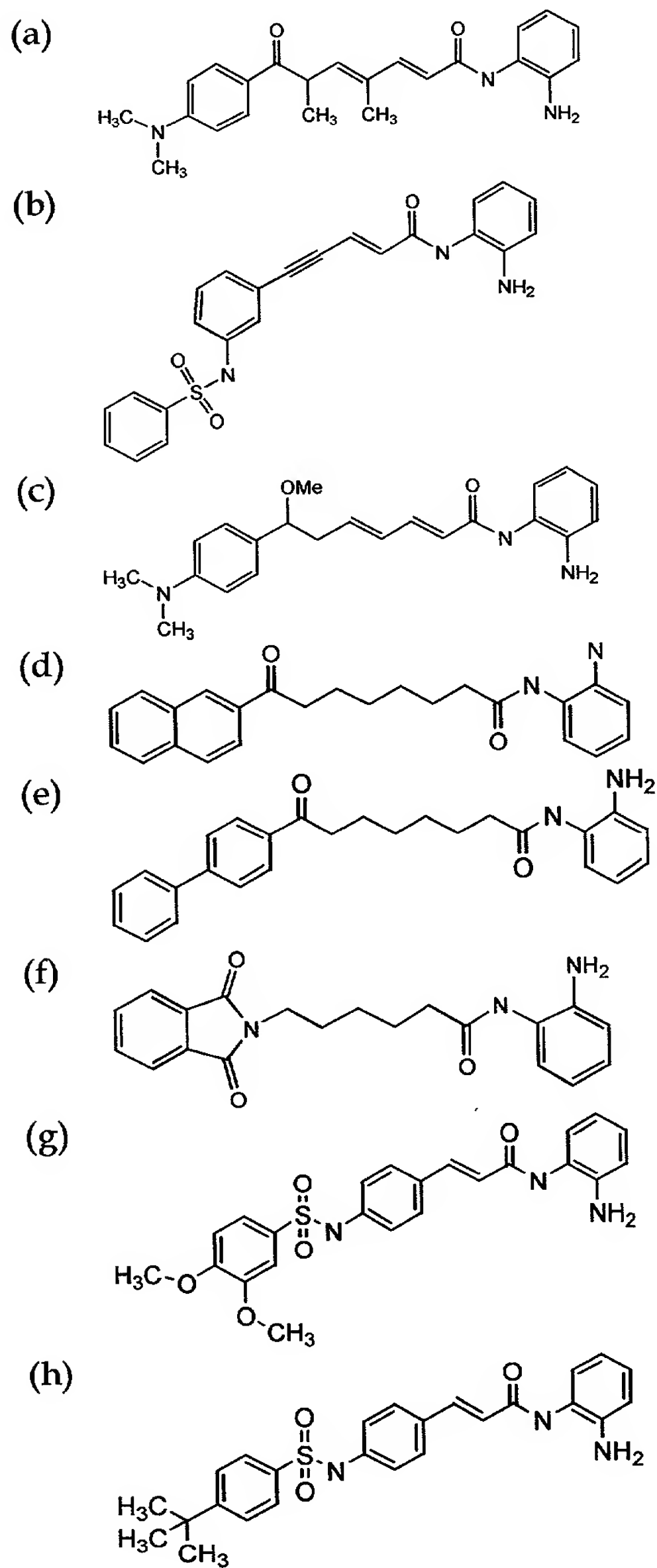
(8) and

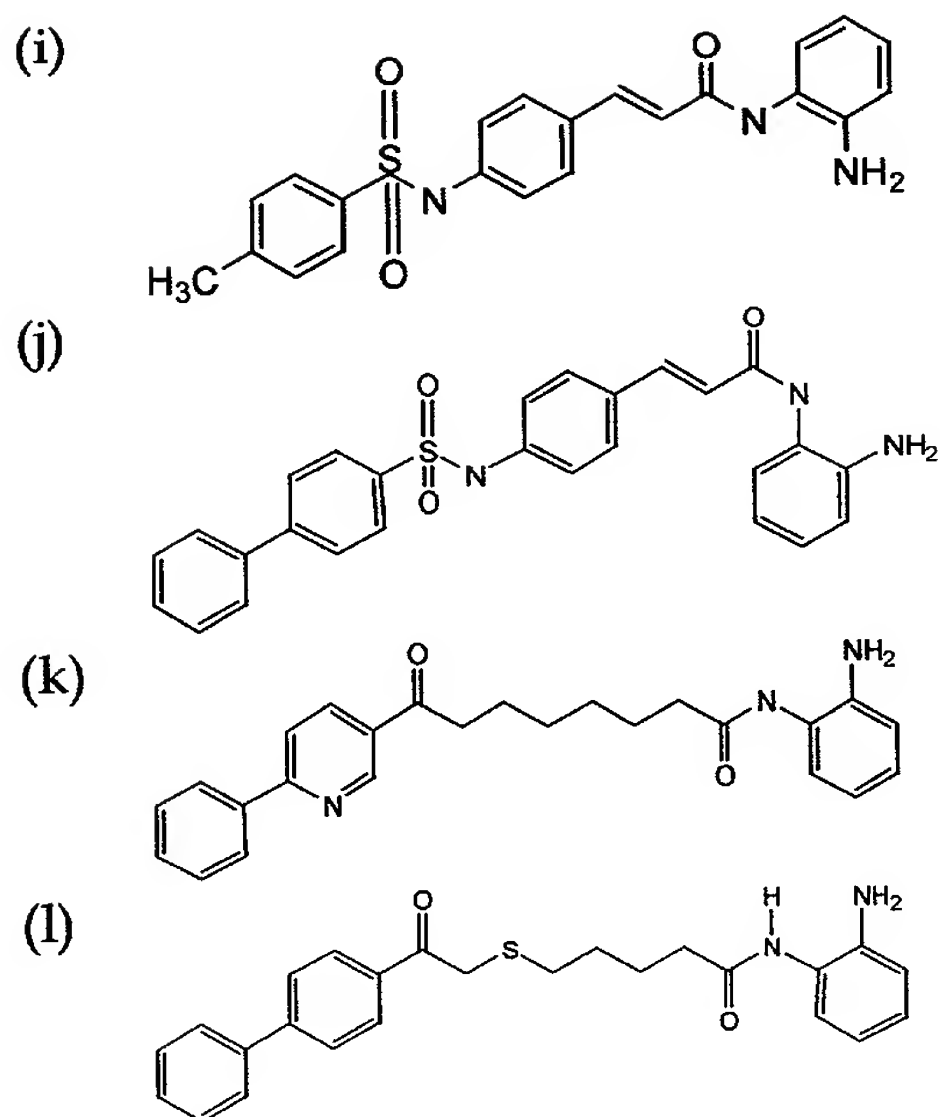


(g)

(9).

57. The composition according to claim 13, wherein the small molecule inhibitor is selected from the group consisting of:





58. A method for inhibiting HDAC-4 activity in a cell, comprising contacting the cell with a specific inhibitor of HDAC-4, whereby HDAC-4 activity is inhibited.

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59. The method according to claim 15, wherein the cell is contacted with a specific inhibitor of HDAC-4 activity selected from the group consisting of:

- (a) an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-4, and
- (b) a small molecule inhibitor of HDAC-4.

60. The method according to claim 16, wherein the specific inhibitor is an antisense oligonucleotide complementary to a region of RNA that encodes a

portion of HDAC-4.

61. The method according to claim 17, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that is a chimeric oligonucleotide.

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62. The method according to claim 17, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that is a hybrid oligonucleotide.

63. The method according to claim 17, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that has a nucleotide sequence length of from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

64. The method according to claim 17, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that has a nucleotide sequence length of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

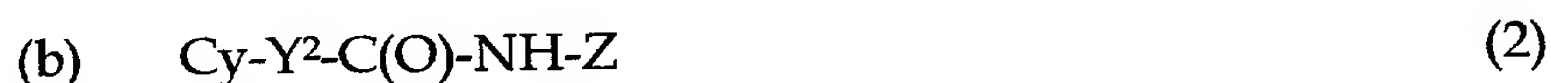
65. The method according to claim 17, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that has a nucleotide sequence length of from about 20 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

66. The method according to claim 17, wherein the cell is contacted with an DHAC-4 antisense oligonucleotide that is SED ID NO:11.

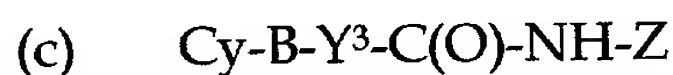
67. The method according to claim 16 wherein the small molecule inhibitor of HDAC-4 has a structure selected from the group consisting of:



5 wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; Y¹ is a C₄ - C₆ alkylene, wherein said alkylene may be optionally substituted and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected from the group consisting of O; NR¹, R¹ being alkyl, acyl or hydrogen; S;
10 S(O); or S(O)₂; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl and -O-M, M being H or a pharmaceutically acceptable cation, wherein the aniliny or pyridyl or thiadiazolyl may be optionally substituted;



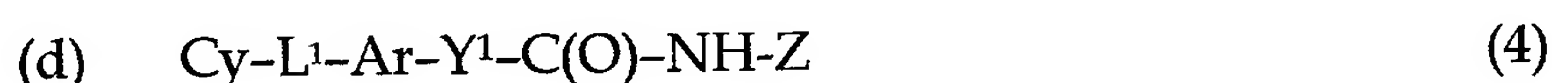
15 wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; Y² is C₅ - C₇ alkylene, wherein said alkylene may be optionally substituted and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected from the group consisting of O; NR¹, R¹ being alkyl, acyl or hydrogen; S;
20 S(O); or S(O)₂; and Z is aniliny or pyridyl, or thiadiazolyl, any of which may be optionally substituted;



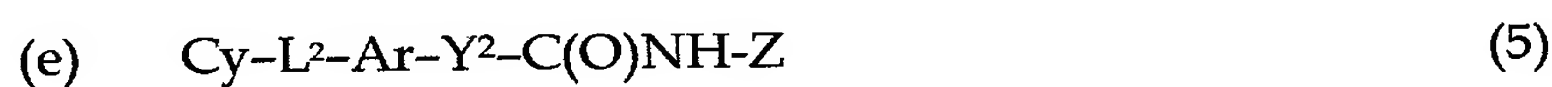
(3)

25 wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; B is selected from the group consisting of -CH(OMe), ketone and methylene; Y³ is a C₄ - C₆ alkylene, wherein said

alkylene may be optionally substituted and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected from the group consisting of O; NR¹, R¹ being alkyl, acyl or hydrogen; S; S(O); or S(O)₂; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl and -O-M, M being H or a pharmaceutically acceptable cation, wherein the aniliny or pyridyl or thiadiazolyl may be optionally substituted;



wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; L¹ is -(CH₂)_m-W-, where m is 0, 1, 2, 3, or 4, and W is selected from the group consisting of -C(O)NH-, -S(O)₂NH-, -NHC(O)-, -NHS(O)₂-, and -NH-C(O)-NH-; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; Y¹ is a chemical bond or a straight- or branched-chain saturated alkylene, wherein said alkylene may be optionally substituted; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl, and -O-M, M being H or a pharmaceutically acceptable cation; provided that when L¹ is -C(O)NH-, Y¹ is -(CH₂)_n-, n being 1, 2, or 3, and Z is -O-M, then Cy is not aminophenyl, dimethylaminophenyl, or hydroxyphenyl; and further provided that when L¹ is -C(O)NH- and Z is pyridyl, then Cy is not substituted indoliny;



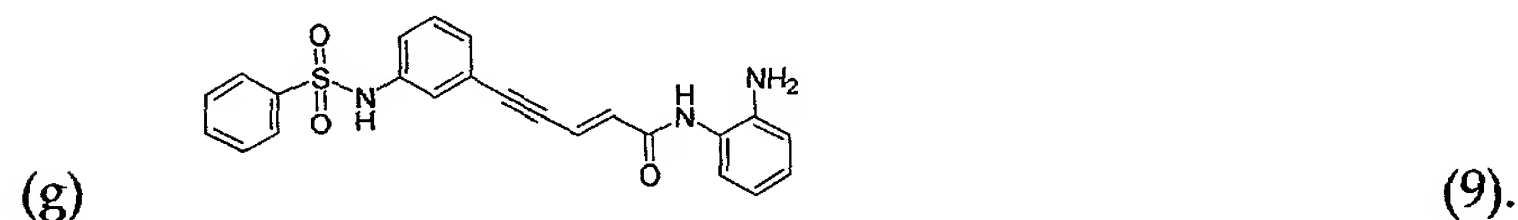
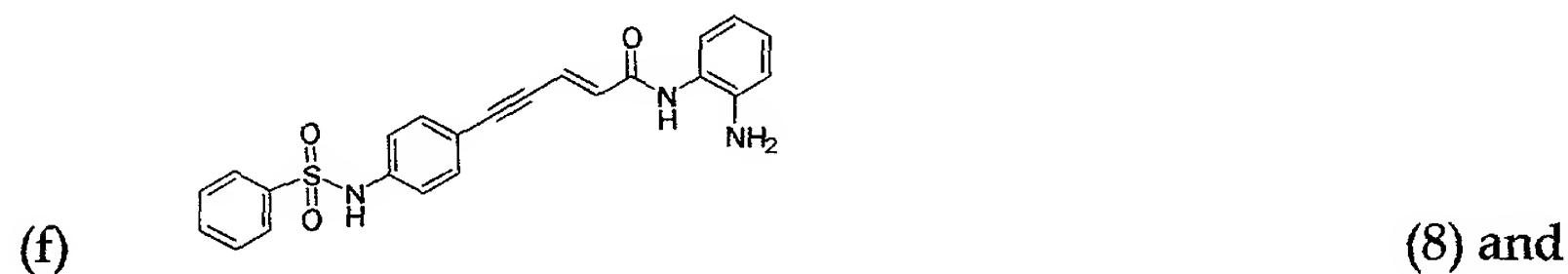
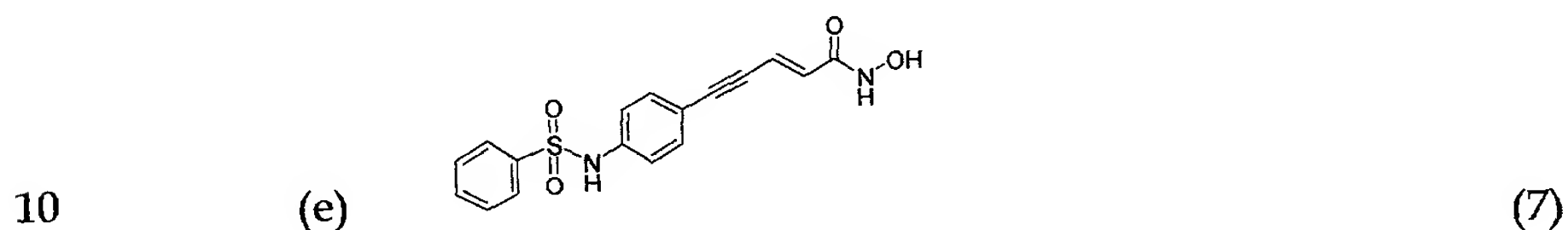
wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted, provided that Cy is not a

(spirocycloalkyl)heterocyclyl; L² is C₁-C₆ saturated alkylene or C₂-C₆ alkenylene, wherein the alkylene or alkenylene optionally may be substituted, provided that L² is not -C(O)-, and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety selected from the group consisting of O; NR', R' being alkyl, acyl, or hydrogen; S; S(O); or S(O)₂; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; and Y² is a chemical bond or a straight- or branched-chain saturated alkylene, which may be optionally substituted, provided that the alkylene is not substituted with a substituent of the formula -C(O)R wherein R comprises an α-amino acyl moiety; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl, and -O-M, M being H or a pharmaceutically acceptable cation; provided that when the carbon atom to which Cy is attached is oxo substituted, then Cy and Z are not both pyridyl;

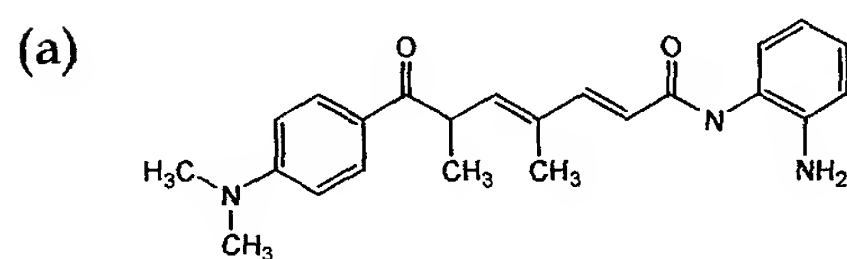
$$(f) \quad \text{Cy-L}^3\text{-Ar-Y}^3\text{-C(O)NH-Z} \quad (6)$$

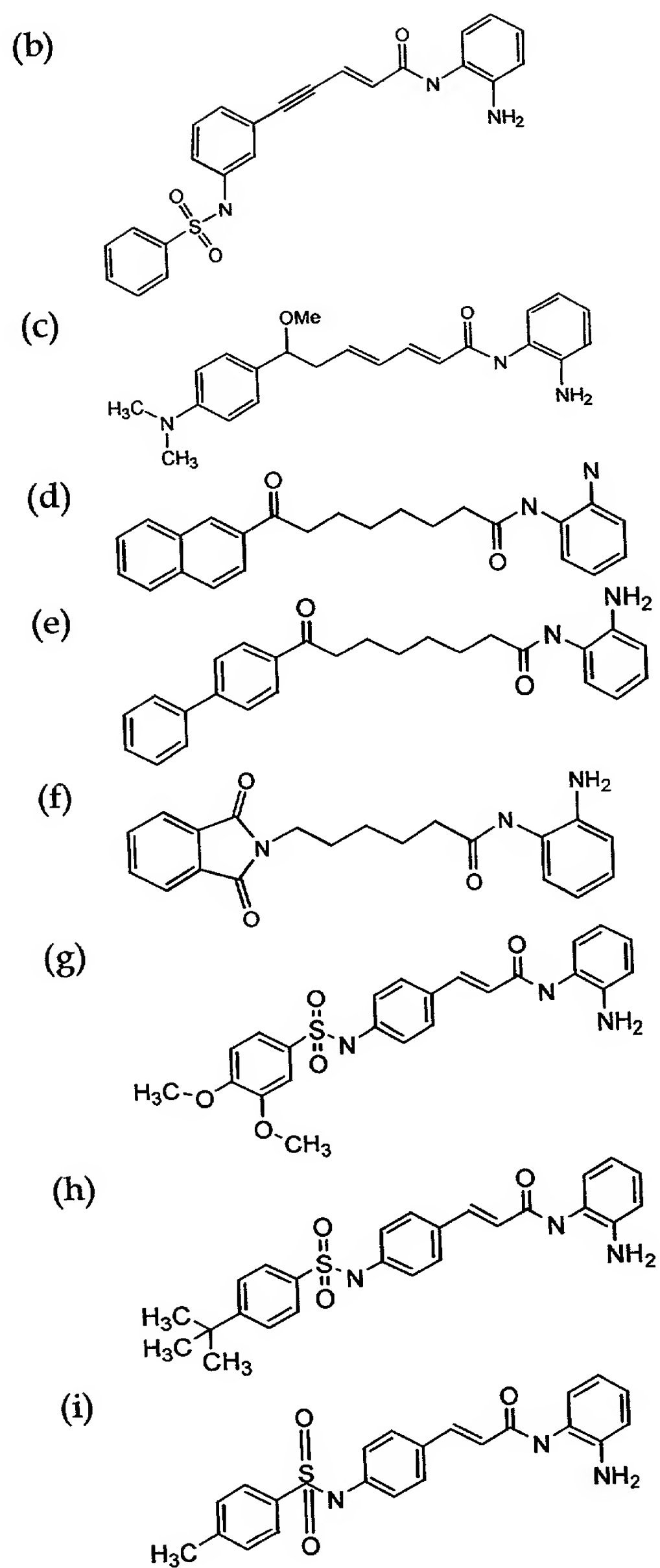
wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted, provided that Cy is not a (spirocycloalkyl)heterocyclyl; L³ is selected from the group consisting of (a) $-(CH_2)_m-W-$, where m is 0, 1, 2, 3, or 4, and W is selected from the group consisting of $-C(O)NH-$, $-S(O)_2NH-$, $-NHC(O)-$, $-NHS(O)_2-$, and $-NH-C(O)-NH-$; and (b) C₁-C₆ alkylene or C₂-C₆ alkenylene, wherein the alkylene or alkenylene optionally may be substituted, provided that L³ is not $-C(O)-$, and wherein one of the carbon atoms of the alkylene optionally may be replaced by O; NR', R' being alkyl, acyl, or hydrogen; S; S(O); or S(O)₂; Ar is arylene, wherein said arylene optionally may be additionally substituted

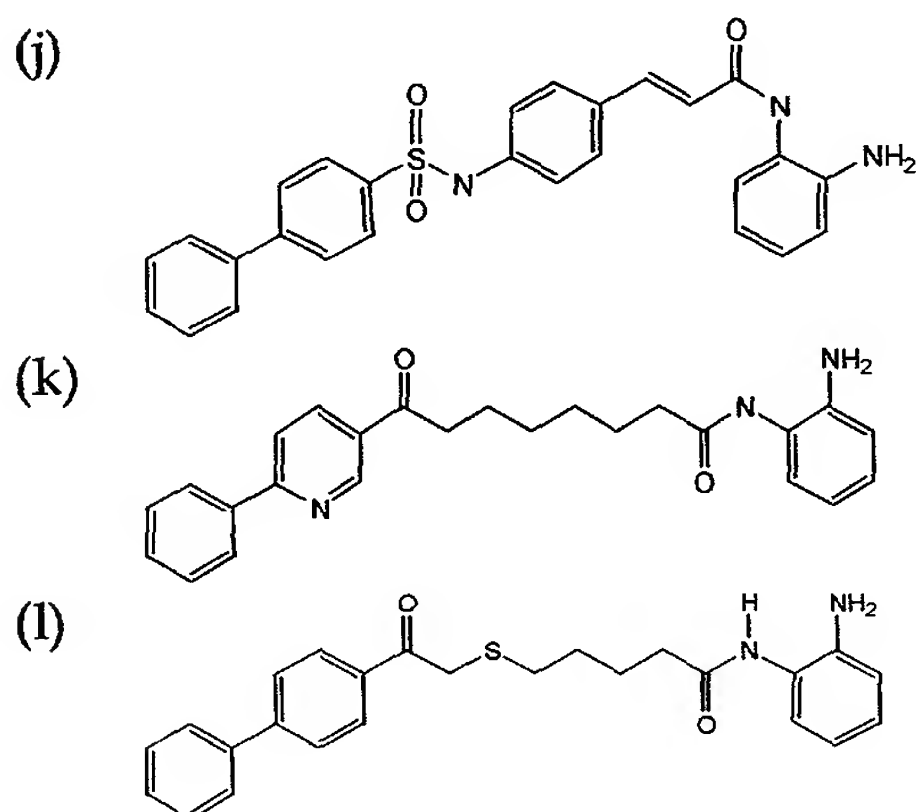
and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; and Y³ is C₂ alkenylene or C₂ alkynylene, wherein one or both carbon atoms of the alkenylene optionally may be substituted with alkyl, aryl, alkaryl, or aralkyl; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl, and -O-M, M being H or a pharmaceutically acceptable cation; provided that when Cy is unsubstituted phenyl, Ar is not phenyl wherein L³ and Y³ are oriented *ortho* or *meta* to each other;



- 15 68. The method according to claim 67, wherein the small molecule inhibitor is selected from the group consisting of:







69. The method according to claim 15, wherein inhibition of HDAC-4 activity in the contacted cell further leads to an inhibition of cell proliferation in the contacted cell.

70. The method according to claim 15, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth retardation of the contacted cell.

71. A method according to claim 15, wherein inhibition of HDAC-4 activity in the contacted cell further leads to growth arrest of the contacted cell.

72. The method according to claim 15, wherein the inhibition of DHAC-4 activity in the contacted cell further leads to programmed cell death of the contacted cell.

73. The method according to claim 26, wherein inhibition of HDAC-4 activity in the contacted cell further leads to necrotic cell death of the contacted cell.

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74. A method for inhibiting neoplastic cell proliferation in an animal, comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of at least one specific inhibitor of HDAC-4, whereby neoplastic cell proliferation is inhibited in the animal.

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75. The method according to claim 31, wherein the animal is administered a specific inhibitor of HDAC-4 selected from the group consisting of:

- 15 (a) an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-4, and
- (b) a small molecule inhibitor.

76. The method according to claim 32, wherein the animal is administered a therapeutically effective amount of an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-4, whereby neoplastic cell proliferation is inhibited in the animal.

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77. The method according to claim 33, wherein the animal is administered a chimeric HDAC-4 antisense oligonucleotide.

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78. The method according to claim 33, wherein the animal is administered a hybrid HDAC-4 antisense oligonucleotide.

5 79. The method according to claim 33, wherein the animal is administered an HDAC-4 antisense oligonucleotide having a nucleotide sequence of from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SED IS NO:4.

10 80. The method according to claim 32, wherein the animal is administered an HDAC-4 antisense oligonucleotide having a nucleotide sequence of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SED IS NO:4.

15 81. The method according to claim 32, wherein the cell is contacted with an HDAC-4 antisense oligonucleotide that has a nucleotide sequence length of from about 20 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:4.

20 82. The method according to claim 32, wherein the animal is administered an HDAC-4 antisense oligonucleotide that is SEQ ID NO:11.

83. The method according to claim 32, wherein a specific inhibitor is a small molecule inhibitor of HDAC-4 having a structure selected from the group consisting of:

25 (a) $\text{Cy-CH(OMe)-Y}^1\text{-C(O)-NH-Z}$ (1)

pyridyl, thiadiazolyl and -O-M, M being H or a pharmaceutically acceptable cation, wherein the anilinyll or pyridyl or thiadiazolyl may be optionally substituted;

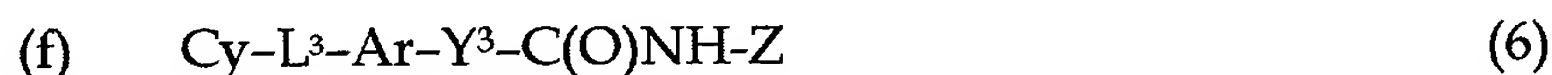


5 wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted; L¹ is -(CH₂)_m-W-, where m is 0, 1, 2, 3, or 4, and W is selected from the group consisting of -C(O)NH-, -S(O)₂NH-, -NHC(O)-, -NHS(O)₂-, and -NH-C(O)-NH-; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be
10 fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; Y¹ is a chemical bond or a straight- or branched-chain saturated alkylene, wherein said alkylene may be optionally substituted; and Z is selected from the group consisting of anilinyll, pyridyl, thiadiazolyl, and -O-M, M being H
15 or a pharmaceutically acceptable cation; provided that when L¹ is -C(O)NH-, Y¹ is -(CH₂)_n-, n being 1, 2, or 3, and Z is -O-M, then Cy is not aminophenyl, dimethylaminophenyl, or hydroxyphenyl; and further provided that when L¹ is -C(O)NH- and Z is pyridyl, then Cy is not substituted indolinyll;



wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted, provided that Cy is not a (spirocycloalkyl)heterocyclyl; L² is C₁-C₆ saturated alkylene or C₂-C₆ alkenylene, wherein the alkylene or alkenylene optionally may be
25 substituted, provided that L² is not -C(O)-, and wherein one of the carbon atoms of the alkylene optionally may be replaced by a heteroatom moiety

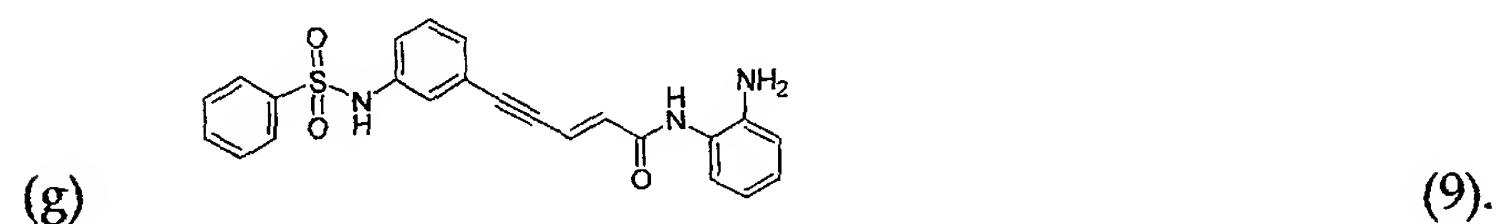
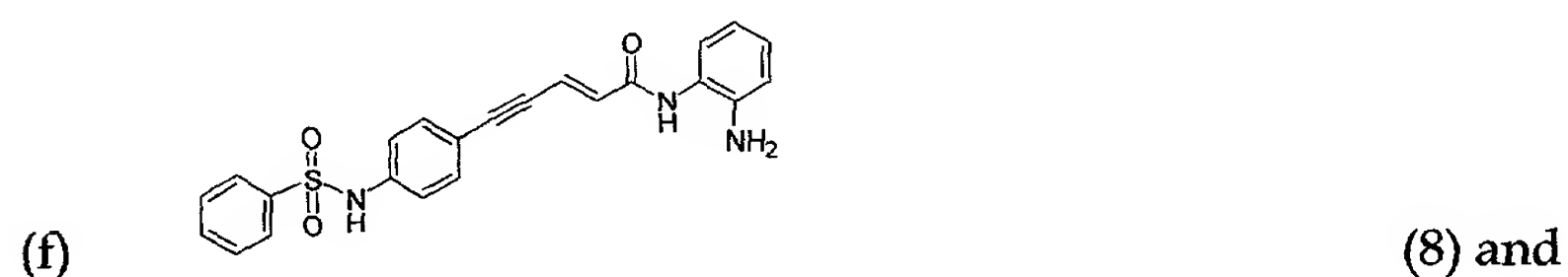
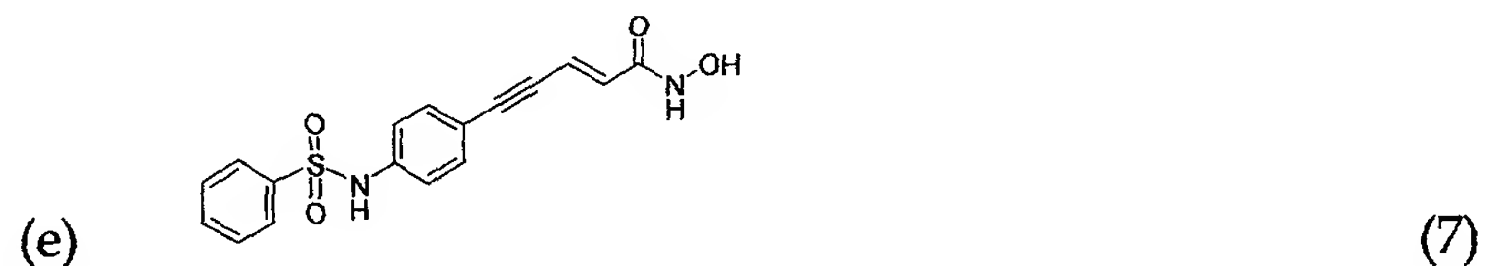
selected from the group consisting of O; NR', R' being alkyl, acyl, or hydrogen; S; S(O); or S(O)₂; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; and Y² is a chemical bond or a straight- or branched-chain saturated alkylene, which may be optionally substituted, provided that the alkylene is not substituted with a substituent of the formula -C(O)R wherein R comprises an α-amino acyl moiety; and Z is selected from the group consisting of aniliny, pyridyl, thiadiazolyl, and -O-M, M being H or a pharmaceutically acceptable cation; provided that when the carbon atom to which Cy is attached is oxo substituted, then Cy and Z are not both pyridyl;



wherein Cy is cycloalkyl, aryl, heteroaryl, or heterocyclyl, any of which may be optionally substituted, provided that Cy is not a (spirocycloalkyl)heterocyclyl; L³ is selected from the group consisting of (a) -(CH₂)_m-W-, where m is 0, 1, 2, 3, or 4, and W is selected from the group consisting of -C(O)NH-, -S(O)₂NH-, -NHC(O)-, -NHS(O)₂-, and -NH-C(O)-NH-; and (b) C₁-C₆ alkylene or C₂-C₆ alkenylene, wherein the alkylene or alkenylene optionally may be substituted, provided that L³ is not -C(O)-, and wherein one of the carbon atoms of the alkylene optionally may be replaced by O; NR', R' being alkyl, acyl, or hydrogen; S; S(O); or S(O)₂; Ar is arylene, wherein said arylene optionally may be additionally substituted and optionally may be fused to an aryl or heteroaryl ring, or to a saturated or partially unsaturated cycloalkyl or heterocyclic ring, any of which may be optionally substituted; and Y³ is C₂ alkenylene or C₂ alkynylene, wherein one or both carbon atoms of the alkenylene optionally

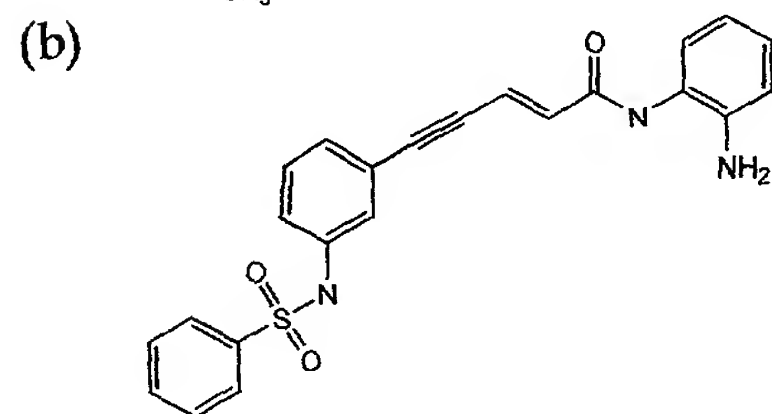
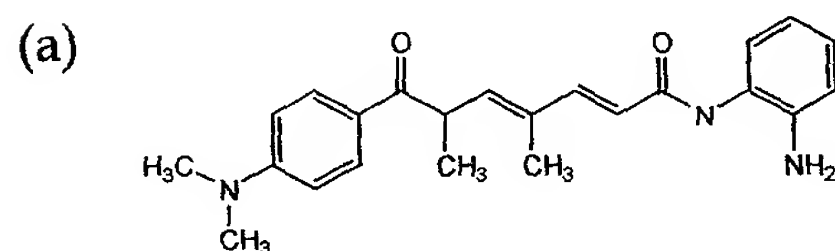
may be substituted with alkyl, aryl, alkaryl, or aralkyl; and Z is selected from the group consisting of aniliny1, pyridyl, thiadiazolyl, and -O-M, M being H or a pharmaceutically acceptable cation; provided that when Cy is unsubstituted phenyl, Ar is not phenyl wherein L³ and Y³ are oriented *ortho* or *meta* to each other;

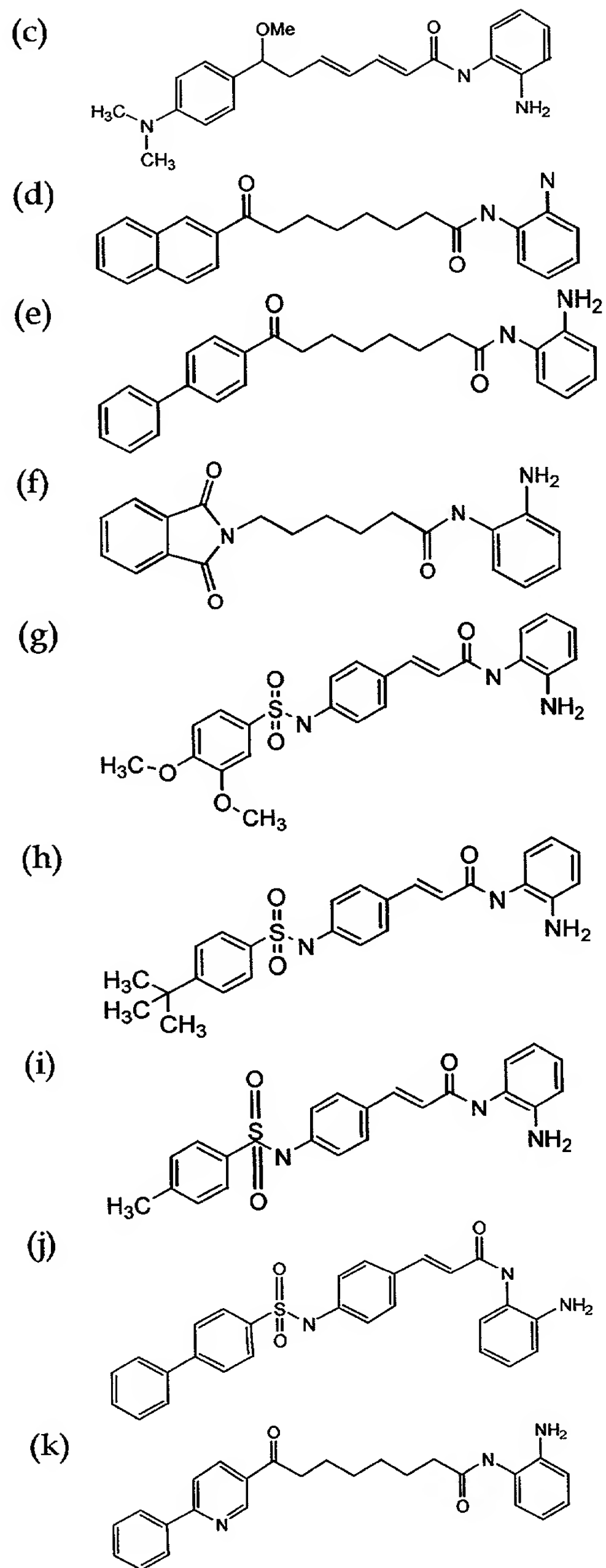
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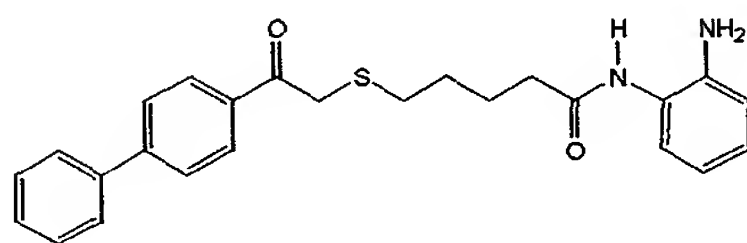
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84. The method according to claim 40, wherein the small molecule inhibitor is selected from the group consisting of:





(1)



85. The method according to claim 32, further comprising administering to an animal a therapeutically effective amount of an antisense oligonucleotide complementary to a region of RNA that encodes a portion of HDAC-1.

86. The method according to claim 42, wherein the animal is administered a chimeric HDAC-1 antisense oligonucleotide.

87. The method according to claim 42, wherein the animal is administered a hybrid HDAC-1 antisense oligonucleotide.

88. The method according to claim 42, wherein the animal is administered an HDAC-1 antisense oligonucleotide having a nucleotide sequence from about 13 to about 35 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:2.

89. The method according to claim 42, wherein the animal is administered an HDAC-1 antisense oligonucleotide having a nucleotide sequence of from about 15 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:2.

90. The method according to claim 42, wherein the animal is administered an HDAC-1 antisense oligonucleotide having a nucleotide

sequence of from about 20 to about 26 nucleotides which is selected from the nucleotide sequence of SEQ ID NO:2.

91. The method according to claim 42, wherein the animal is
5 administered an HDAC-1 antisense oligonucleotide that is SEQ ID NO:5.